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Original Scientific Paper

DOPPLER SONOGRAPHIC, ELECTROENCEPHALOGRAPHIC AND COGNITIVE CHANGES IN INDIVIDUALS WITH CORTICAL CEREBRAL ATROPHY YOUNGER THAN SIXTY

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SUMMARY – The aim of the study was to investigate Doppler sonographic, electroencephalographic and cognitive changes in patients with cortical cerebral atrophy younger than 60. Sixty individuals aged 60 years and younger with cortical cerebral atrophy detected by qualitative methods on CT scan (experimental group), and 60 subjects with normal endocranial CT scan (control group) were enrolled and matched according to age, sex and education level. Mean blood flow velocities (MBFV), resistance index (RI) and pulsatility index (PI) were measured by transcranial Doppler sonography (TCD). Electroencephalography (EEG) was done with calculation of the percent frequency of electroencephalographic waves. Tests of cognitive functions were performed with Mini Mental Status Examination (MMSE) and Wechsler Memory Scale. MBFV were significantly decreased in subjects with cortical cerebral atrophy compared with the control group ($p<0.0001$): middle cerebral artery 53 cm/s (experimental) *vs.* 65 cm/s (control group); anterior cerebral artery 38 *vs.* 49 cm/s; posterior cerebral artery 34 *vs.* 39 cm/s; and basilar artery 35 *vs.* 43.5 cm/s. Doppler sonography measures of RI and PI showed both parameters to be considerably higher in subjects with cortical cerebral atrophy in all arteries ($p<0.001$). Analysis of the percent frequency of electroencephalographic waves showed a significantly higher frequency of the slow delta and theta waves in individuals with cortical cerebral atrophy than in the control group (21% *vs.* 5.6% and 11.5% *vs.* 3.7%; $p<0.0001$). MMSE and Wechsler Memory Scale scores were considerably lower in patients with cortical cerebral atrophy compared with the control group (26.3 *vs.* 29.0 and 97 *vs.* 125; $p<0.0001$). Cognitive changes were not dependent of age and sex, but did depend on education level. Accordingly, Doppler sonographic, EEG and cognitive changes in middle-aged individuals with cortical cerebral atrophy are somewhat between normal findings and findings in patients with early dementia. Long-term follow up of these individuals and periodical monitoring of cognitive status, TCD and EEG are needed.

Key words: *Cognition disorders – diagnosis; Cognition disorders – ultrasonography; Electroencephalography; Dementia, vascular – diagnosis*

Introduction

Cortical and subcortical cerebral atrophy is associated with normal aging. Neuropathologic observations have shown that cerebrocortical atrophy in normal aging is based on the loss of cortical and subcortical neurons accompanied by axonal dropout in the white matter, and this is compatible with the description of neural apoptosis[1]. The main neuroimaging features on both computed tomography (CT) and magnetic resonance imaging (MRI) are symmetric ventricular enlargement, widening of the cerebral sulci and fissures, and enlargement of the subarachnoid space, and these qualitative parameters can be used as a subjective method in the detection of cerebral atrophy[2]. However, this kind of assessment is highly dependent on the rater's experience and has a low inter-observer reliability[3].

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Transcranial Doppler sonography (TCD) is a noninvasive ultrasound technique of examining the brain main blood vessels, their chemodynamics as well as possible functional changes. Although TCD is primarily used to recognize intracranial stenosis and occlusions, to detect and monitor cerebral vasospasm after subarachnoid hemorrhage, and to record chemodynamic changes in certain diseases (e.g., migraine), this procedure has also been used to follow blood flow changes associated with normal aging[4].

Electroencephalography (EEG) is a technique for the measurement of spontaneous brain electrical activity. EEG is the most useful laboratory test to help establish the diagnosis of epilepsy, and can be an important diagnostic tool in different types of dementia and encephalopathies. Furthermore, EEG can play a role in the diagnosis of structural brain lesions[5].

With the older segment of the population growing at an increasingly rapid rate, the issue of cognitive impairment has become a common concern for patients, their families and clinicians. Many elderly individuals are concerned about subtle cognitive impairments which can, to a greater or lesser extent, influence normal functioning. Several aspects of cognition have been studied more extensively than others, but memory and attention are likely to decline to a certain extent with normal aging[6].

The aim of the study was to investigate TCD, EEG and cognitive changes in patients with cortical cerebral atrophy younger than 60.

Subjects and Methods

Sixty consecutive individuals aged 60 and younger, with cortical cerebral atrophy detected by qualitative methods on CT scan (experimental group), and 60 persons with normal endocranial CT scan (control group) were enrolled in the study and matched according to age, sex and education level. In each group there were 28 (43%) men, mean age 49.5±5.3 years. The subjects in both groups were neurologically intact and complained of headaches, dizziness and/or vertigo, and with no history of cerebrovascular disease, tumor, severe head trauma, epilepsy, mental retardation, or chronic psychiatric disease. In case of any focal pathology on CT, the subject was excluded.

All CT scans were obtained at Tuzla Departement of Radiology, on a spiral CT scanner (Siemens ELSCINT Twin, Siemens) with contiguous 1-cm transaxial slices. After subjective assessment of the presence of cortical cerebral atrophy on CT scan, linear CT measurements were done in all subjects (frontal fissure index, sylvian fissure index, index 4 cortical sulci, and inverse cella media index) according to Gomori *et al.*[7]. Investigation of linear indexes showed significant differences for all parameters between patients with CT confirmed cortical cerebral atrophy and control subjects with normal endocranial CT (Table 1).

Using standard technical procedures, TCD was performed in all patients at Tuzla Department of Neurology. TCD was performed using a DWL-Multi-Dop 4 machine (DWL, Germany) with automatic processing and a probe of 2 MHz. Test conditions were similar to those described previously, with the subject lying in supine decubitus and in somatosensory rest, locating the TCD probe on the temporal and suboccipital window[8]. Sonography of the middle (MCA), anterior (ACA) and posterior (PCA) cerebral arteries was performed by transtemporal approach, and of the basilar artery (BA) by transforaminal approach. Positive identification of the previously mentioned arteries was achieved using standardized criteria[4,8], and mean blood flow velocities (MBFV), resistance index (RI) and pulsatility index (PI) were measured.

All EEG recordings were carried out by using a 16-channel electroencephalograph (Medelec Examiner Vickers, Holland) and electrodes were applied to the scalp

Table 1. Linear computed tomography measurements

	Experimental group		Control group		p-value
	Value	SD	Value	SD	
FFI	7.5	±1.5	2.8	±1.0	<0.0001
SFI	7.7	±1.5	3.0	±0,9	<0.0001
4 CSI	14.0	±3.0	7.0	±1.4	<0.0001
CMI	22.5	±3.3	19.0	±2.2	<0.0001

FFI=frontal fissure index; SFI=sylvian fissure index; 4 CSI=four cortical sulci index; CMI=cella media index

Table 2. Mean blood flow velocity in cerebral arteries

Artery	Mean blood flow velocity – cm/s (SD)	
	Experimental group	Control group
MCA lef	51.0 (±8.0)*	65.0 (±7.5)
MCA right	54.0 (±8.0)*	65.0 (±8.0)
ACA left	37.0 (±7.0)*	49.0 (± 5.5)
ACA right	38.0 (±7.0)*	49.0 (± 5.0)
PCA left	33.0 (±4.0)*	38.0 (±3.5)
PCA right	34.0 (±4.5)*	39.0 (±5.0)
BA	35.0 (±7.0)*	43.5 (±7.0)

MCA=middle cerebral artery; ACA=anterior cerebral artery; PCA=posterior cerebral artery; BA=basilar artery; SD=standard deviation; *p<0.001

according to the international 10-20 system. For statistical analysis we used 15 seconds of the recording material without artifacts (5 seconds with eyes closed, 5 seconds with eyes open, and 5 seconds after routine 3-minute hyperventilation). After sampling at a rate of 128 Hz and analog-to-digital conversion, fast Fourier analysis was performed. The total EEG frequency range of analysis was 0.5-32 Hz, and the EEG relative power was calculated for the delta (0.5-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.0-12.9 Hz) and beta (13.0-32.0 Hz) frequency bands.

Five individuals were taking small doses of benzodiazepines (3 in the experimental group and 2 in the control group). These subjects had a drug washout period of 48 hours before EEG studies.

We calculated the frequency (percentage) for the EEG waves in each modality (eyes closed, eyes open, after hyperventilation), and mean values were used in further analysis. The following EEG measures were calculated: mean frequency (percentage) of total power *per* frequency band and the average of relative power for each of the four cerebral quadrants: left anterior (F3, F7, T3, C3), right anterior (F4, F8, T4, C4), left posterior (P3, T5, O1), and right posterior (P4, T6, O2) (Fig. 1).

Tests of cognitive functions (orientation, registration, attention, calculation, recall, language, praxia, and memory) were performed with the Mini Mental Status Examination (MMSE) and Wechsler Memory Scale (WMS).

All procedures (TCD, EEG, MMSE and WMS) and reading of the results were carried out by readers in order to blind CT findings. Statistical analysis was performed by *t*-test; statistical significance was set at p<0.05.

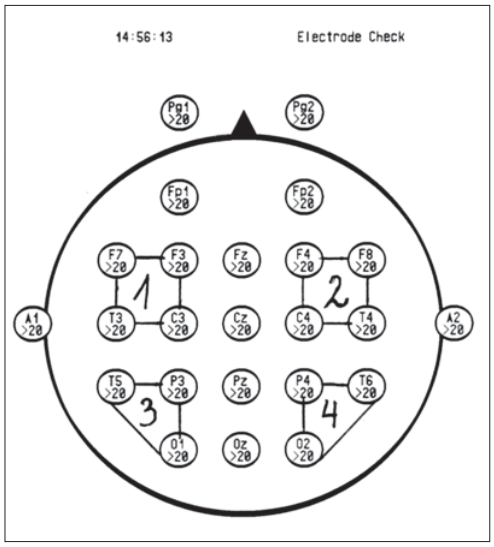
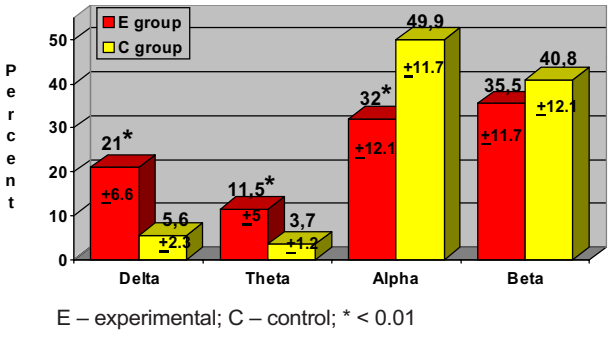


Fig 1. Scheme of the international 10-20 system with cerebral quadrants: 1. left anterior 2. right anterior 3. left posterior 4. right posterior

Results

MBFV measured by transcranial Doppler sonography were significantly decreased in subjects with cortical cerebral atrophy in both arteries of anterior and posterior cerebral circulation and basilar artery, compared with the control group (Table 2). Differences in MBFV were symmetrical in all arteries and with no differences between the right and left brain hemispheres.

Doppler sonographic RI and PI measures showed both parameters to be much higher in subjects with cortical cerebral atrophy compared with those with normal endocranial CT findings in all arteries of cerebral circulation (Table 3). RI was between 0.59 and 0.61 in the experimental group, and between 0.50 and 0.55 in the control group. Additionally, PI was between 0.88 and 0.97



E – experimental; C – control; * < 0.01

Fig 2. Frequency of electroencephalographic waves

Table 3. Values of resistance and pulsatility indices in cerebral arteries

	Resistance index		Pulsatility index	
Artery	E group	C group	Group	C group
MCA right	0.59 (±0.07)*	0.51 (±0.06)	0.89 (±0.10)*	0.75 (±0.08)
MCA left	0.60 (±0.07)*	0.50 (±0.04)	0.88 (±0.10)*	0.74 (±0.09)
ACA right	0.60 (±0.06)*	0.54 (±0.06)	0.96 (±0.10)*	0.78 (±0.07)
ACA left	0.61 (±0.06)*	0.53 (±0.06)	0.97 (±0.16)*	0.78 (±0.08)
PCA right	0.61 (±0.07)*	0.55 (±0.06)	0.95 (±0.20)*	0.81 (±0.09)
PCA lef	0.61 (±0.06)*	0.55 (±0.05)	0.96 (±0.14)*	0.80 (±0.09)
BA	0.60 (±0.07)*	0.54 (±0.04)	0.92 (±0.15)*	0.78 (±0.10)

MCA=middle cerebral artery; ACA=anterior cerebral artery; PCA=posterior cerebral artery; BA=basilar artery; E=experimental; C=control; *p<0.001

in the subjects with cortical cerebral atrophy, and between 0.75 and 0.81 in the subjects with normal CT.

Analysis of the frequency percentage of electroencephalographic waves showed a significantly higher frequency of the slow delta and theta waves in cortical cerebral atrophy than in the control group (21% *vs.* 5.6% and 11.5% *vs.* 3.7%, respectively; p<0.0001) (Fig. 2). On the other hand, the individuals in the experimental group had a considerably lower frequency of the alpha and beta waves compared with the subjects with normal CT.

Differences in the distribution of EEG waves were recorded in all cerebral quadrants without asymmetry according to the side (left-right), and these differences did not depend on age, sex or education level (Table 4). The frequency of delta and theta waves was much higher in the experimental group compared with matched controls in all quadrants, while the subjects with cortical

Table 4. Relative frequency (%) of electroencephalographic waves for the four cerebral quadrants

	Left anterior quadrant		Right anterior quadrant	
EEG waves	**E group**	C group	**E group**	C group
Delta	**22.3***	6.6	**± 9.9**	± 3.6
	22.6*	6.1	**± 8.4**	± 3.3
Theta	**11.6***	4.0	**± 5.5**	± 1.7
	10.9*	3.7	**± 5.8**	± 1.6
Alpha	**25.2***	41.3	**±12.7**	±13.1
	25.8*	42.2	**±13.7**	±13.6
Beta	**40.9**	48.1	**±14.2**	±13.0
	40.7	48.0	**±14.2**	±13.4

	Left posterior quadrant		Right posterior quadrant	
EEG waves	**E group**	C group	**E group**	C group
Delta	**19.0***	4.1	**± 9.2**	± 2.0
	17.8*	5.0	**± 9.2**	± 2.0
Theta	**13.1***	3.5	**± 6.5**	± 1.5
	12.2*	3.5	**± 5.4**	± 1.4
Alpha	**37.4***	56.7	**±15.7**	±13.3
	40.0*	56.9	**±15.0**	±13.0
Beta	**30.5**	35.7	**±15.1**	±13.4
	30.0	34.6	**±13.5**	±13.3

E=experimental; C=control; *p<0.001

atrophy had a significantly lower frequency of alpha waves. There were no between-group differences in the distribution of beta EEG waves in four cerebral quadrants.

Both MMSE and WMS scores were considerably lower in patients with cortical cerebral atrophy than in the control group (26.3 *vs*. 29.0 and 97 *vs*. 125, respectively; $p<0.0001$) (Fig. 3). This difference was not dependent on age and sex but did depend on education level, i.e. differences in MMSE and WMS were not significant in subjects with higher education level (Table 5).

Discussion

The evidence of a correlation between cerebral blood flow detected by the xenon-133 method, and flow velocity variation revealed by TCD provide a theoretical basis for the investigation of intracranial vascular reactivity with TCD in normal aging, cognitive impairment and dementia. Several investigators have pointed out that MBFV decreases with age. On the other hand, Provinciali *et al*.[9] found lower rest MBFV and higher PI in patients with vascular dementia than in patients with Alzheimer disease and age-matched controls. Other authors report significantly decreased MBFV and increased PI and RI in both vascular dementia and Alzheimer disease compared to healthy elderly controls[10]. Our results (Tables 2 and 3) showed that individuals with cortical cerebral atrophy had significantly lower MBFV, and higher PI and RI compared with age-, sex- and education level-matched controls. These changes could not be considered as having resulted from aging because our subjects with cortical atrophy were aged 60 and younger, and some authors report that cerebral blood flow is not diminished in normal aging despite age-related cerebral atrophy[11]. TCD findings in the subjects with cortical cerebral atrophy in this study, as compared with previously cited studies, fell between normal findings and findings in various types of dementia. It is an open question whether the individuals with cortical atrophy and these TCD changes are candidates for the development of cerebrovascular insufficiency or dementia.

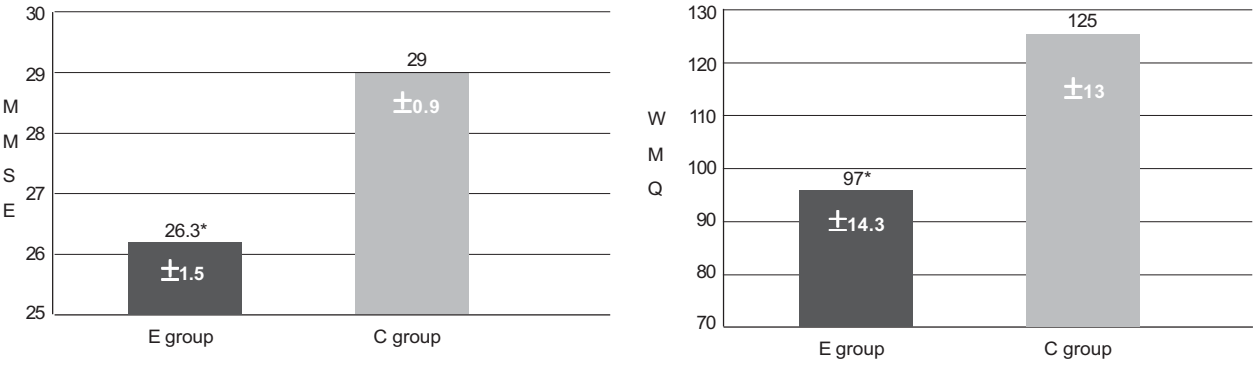
EEG changes in normal aging are nonspecific and it is still a matter of debate whether they are the result of aging or pathologic changes in the nervous system. Jelic *et al*.[12] found that quantitative EEG could give important information for the possible prediction of Alzheimer disease in patients with mild cognitive impairment. Grunwald *et al*.[13] report a significant negative linear correlation between theta power over frontal regions and atrophy in mild cognitive impairment and mild dementia. Results of another study suggest that alpha activity on EEG is most closely linked to cognitive function and rCBF, while beta and theta activity more likely reflect lower cortical or subcortical changes in early Alzheimer disease[14]. In our study, EEG changes in individuals with cortical cerebral atrophy (Fig. 2 and Table 4) were similar to but less pronounced than findings in mild cognitive impairment and early dementia.

The basic characteristic of all dementias and most other neurodegenerative diseases is impairment of the normal cognitive functioning. Discussion on memory as the most sensitive index of the development of dementia raises the question of an intermediate transitional phase between normal cognitive functioning and dementia. Petersen *et al*.[15] followed-up 66 individuals with mild cognitive impairment for up to 54 months. In the first 18 months, dementia developed in 20%, at 36 months in

Table 5. Mini Mental Status Examination and Wechsler Memory Scale in study groups according to age, sex, and education level

		Experimental group		Control group		Experimental group		Control group	
		MMSE	SD	MMSE	SD	Quotient	SD	Quotient	SD
Age (yrs)	≤50	27.0	±1.8•	29.1	±0.9	100	±14.0•	124	±12.0
	>50	26.2	±1.7•	28.9	±1.0	95	±14.4•	126	±14.3
Sex	Man	26.2	±2.2°	29.1	±0.9	99	±16.9•	128	±13.8
	Woman	26.5	±1.4•	28.1	±0.9	96	±11.9•	123	±12.0
Education	(8 yrs)	25.5	±2.0°	28.4	±1.0	91	±11.0•	113	±8.6
	(≤12 yrs)	26.6	±1.6•	29.0	±0.9	94	±11.3•	125	±11,0
	(≥12 yrs)	28.4	±1.1⊕	29.0	±0.6	117	±11.1⊕	130	±10.1

• $p<0.0001$ ∘ $p<0.001$ ⊕ $p=0.05$



MMSE = Mini Mental Status Examination; WMQ = Wechsler Memory Quotient; E=experimental; C=control; *p<0.001

Fig 3. Mini Mental Status and Wechsler Memory Scale in study groups

40%, and at 5 years in more than 50% of patients. MMSE in patients with mild cognitive impairment on baseline test was 26, and Wechsler memory quotient was 96, which is very similar to the results of the same tests in subjects with cortical cerebral atrophy recorded in our study (Fig. 3).

Meguro *et al*.[16] have reported that the extent of brain atrophy correlated with age and education level, and brain atrophy was more prominent in the lower educated group, therefore, the authors suggest that education might have a protective effect on cognitive changes. In our study, patients with cortical cerebral atrophy and high education level had lower results on MMSE and Wechsler Memory Scale compared to matched controls, but the differences were not significant. Therefore, for more precise evaluation of cognitive functions in these patients other neuropsychological tests are required[17].

Conclusion

Individuals with cortical cerebral atrophy younger than 60 have decreased MBFV measured by TCD, higher RI and PI, and higher frequency of the slow delta and theta EEG waves. These subjects have cognitive changes as evaluated by Mini Mental Status Examination and Wechsler Memory Scale. Cognitive changes are not dependent on age and sex but are lower in patients with high education level.

Doppler sonographic, EEG and cognitive changes in middle-aged individuals with cortical cerebral atrophy fall between normal findings and findings in patients with early dementia. Long-term follow up of these individuals and periodic monitoring of cognitive status, TCD and EEG are needed.

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Sažetak

PROMJENE NALAZA DOPPLEROVE SONOGRAFIJE, ELEKTROENCEFALOGRAFIJE I SPOZNAJNE FUNKCIJE U OSOBA MLAĐIH OD ŠEZDESET GODINA S ATROFIJOM MOŽDANE KORE

Dž. Smajlović, O. Sinanović, M. Vidović, O. Ibrahimagić, S. Pavlović, S. Sarihodžić i *M. Šahimpašić*

Cilj studije bio je ispitati promjene u nalazu Dopplerove sonografije, elektroencefalografije (EEG) i spoznajnoj funkciji u bolesnika mlađih od 60 godina s atrofijom moždane kore. U studiju je bilo uključeno 60 osoba u dobi od 60 godina i mlađih s atrofijom moždane kore otkrivenom kvalitativnim metodama pomoću CT (eksperimentalna skupina) i 60 osoba s normalnim endokranijskim CT nalazom podjednake dobi, spola i razine obrazovanja. Transkranijskom Dopplerovom sonografijom (TCD) mjerene su srednje brzine krvnog protoka (MBFV), indeks otpornosti (RI) i indeks pulsatilnosti (PI). EEG je provedena uz izračunavanje postotka učestalosti elektroencefalografskih valova. Testovi spoznajnih funkcija provedeni su pomoću *Mini Mental Status Examination* (MMSE) i *Wechsler Memory Scale*. MBFV su bile značajno niže u osoba s atrofijom moždane kore u usporedbi s kontrolnom skupinom ($p<0,0001$): u srednjoj moždanoj arteriji 53 cm/s (eksperimentalna skupina) prema 65 cm/s (kontrolna skupina); u prednjoj moždanoj arteriji 38 prema 49 cm/s; u stražnjoj moždanoj arteriji 34 prema 39 cm/s; i u bazilarnoj arteriji 35 prema 43,5 cm/s. Mjerenja RI i PI Dopplerovom sonografijom pokazala su znatno više vrijednosti obaju parametara u ispitanika s atrofijom moždane kore u svim arterijama ($p<0,001$). Analiza postotne učestalosti elektroencefalografskih valova pokazala je značajno višu učestalost polaganih delta i teta valova u osoba s atrofijom moždane kore nego u kontrolnoj skupini (21% prema 5,6%, odnosno 11,5% prema 3,7%; $p<0,0001$). Rezultati MMSE i *Wechsler Memory Scale* bili su znatno niži u bolesnika s atrofijom moždane kore u usporedbi s kontrolnom skupinom (26,3 prema 29,0, odnosno 97 prema 125; $p<0,0001$). Spoznajne promjene nisu ovisile o dobi i spolu, ali su bile ovisne o razini obrazovanja. Zaključeno je kako se promjene u nalazu Dopplerove sonografije, EEG i spoznajnoj funkciji kreću između normalnih nalaza i nalaza u bolesnika s ranom demencijom. U ovih osoba potrebno je dugoročno praćenje i povremeno motrenje spoznajne funkcije te nalaza TCD i EEG.

Ključne riječi: *Poremećaji spoznajne funkcije – dijagnostika; Poremećaji spoznajne funkcije – ultrasonografija; Elektroencefalografija; Demencija, vaskularna – dijagnostika*